American Journal of Medical Genetics 69:418–421 (1997)

Brief Clinical Report

Goldenhar Complex: A Further Case With Uncommon Associated Anomalies

Leopoldo Zelante,[1]* Paolo Gasparini,[1] Alessandro Castriota Scanderbeg,[2] Lucia Dimitri,[3] Marco Criconia,[4] and Robert J. Gorlin[5]

[1]*Medical Genetics Service, IRCCS-CSS Hospital, San Giovanni Rotondo, Italy*
[2]*Department of Radiology, IRCCS, S. Lucia, Roma, Italy*
[3]*Pathology Unit IRCCS-CSS Hospital, San Giovanni Rotondo, Italy*
[4]*Department of Cardiology, IRCCS-CSS Hospital, San Giovanni Rotondo, Italy*
[5]*School of Dentistry, University of Minnesota, Minneapolis*

We report on a further case of Goldenhar complex with uncommon and clinically remarkable associated anomalies. This additional case increases the number of observations and descriptions of patients with "expanded Goldenhar complex." Pathogenetic aspects are discussed. Am. J. Med. Genet. 69:418–421, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: Goldenhar complex; hydrocephalus; limb anomalies; congenital heart disease

INTRODUCTION

The oculo-auriculo-vertebral complex was originally described as a nonrandom association of auricular, vertebral, and ocular defects. The facial phenotype is characteristic and defined as hemifacial microsomia. The range of clinical manifestations has been extended to other organ systems apparatus, and a variety of terms have been used to describe this condition [Gorlin et al., 1990].

Here, we report on a further case associated with uncommon, clinically remarkable anomalies.

CLINICAL REPORT

The proposita is the second child of a 28-year-old mother and her non-consanguineous 33-year-old husband. She was born at term of a pregnancy complicated by polyhydramnios. At birth, Apgar scores were 2 and 5, at 1 min and 5 min, respectively. Birthweight was 2,700 g (10th centile), length 46.5 cm (3rd centile), and head circumference (OFC) 35.4 cm (50th centile). Immediately noted were facial asymmetry, more evident when the baby cried, preauricular tags on the right side, and severe hypoplasia of the left forearm with oligodactyly (Fig. 1). Karyotype was 46,XX. The patient died after 45 days because of cardiac impairment.

Roentgenograms showed facial asymmetry with mild mandibular and malar hypoplasia of the left side. Shortness of the left upper limb, short humerus, and hypoplasia of the ipsilateral scapula were detected. Left radial ray deficiency, short forearm, and absence of radius and thumb were associated with a clubbed and radially deviated hand. Absence of the phalanges of the fourth digit and of the second ray were also noted (Fig. 2). Other findings included dorsal hemivertebra at C3, lateral hemivertebra at C7, and kyphoscoliosis (Fig. 3).

Cerebral sonography showed a mild dilatation of the lateral ventricles. The temporal and occipital horns were particularly involved, the right ventricle being larger than the left (Fig. 4).

A complex congenital heart defect was also detected on sonographic examination. Double-outlet right ventricle communicating with a small vestigial ventricular

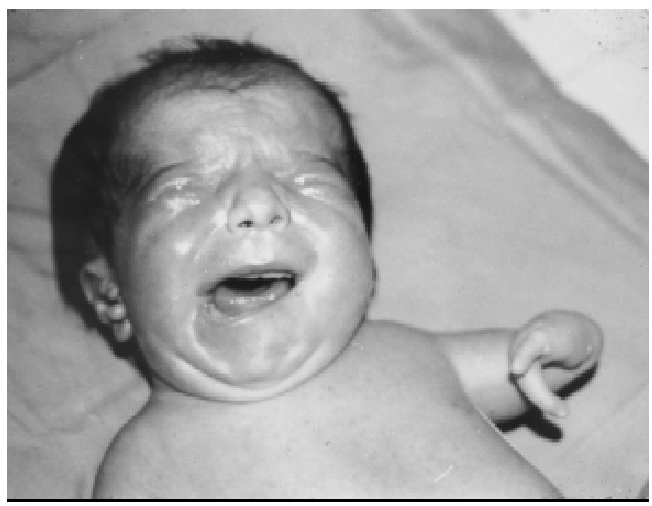

Fig. 1. Facial asymmetry, preauricular tags, and malformed left forearm of the patient.

Contract grant sponsor: Associazione Italiana per lo Studio delle Malformazioni.

*Correspondence to: Dr. Leopoldo Zelante, Medical Genetics Service, IRCCS-CSS Hospital, I-71013 San Giovanni Rotondo, Italy.

Received 3 January 1996; Accepted 2 April 1996

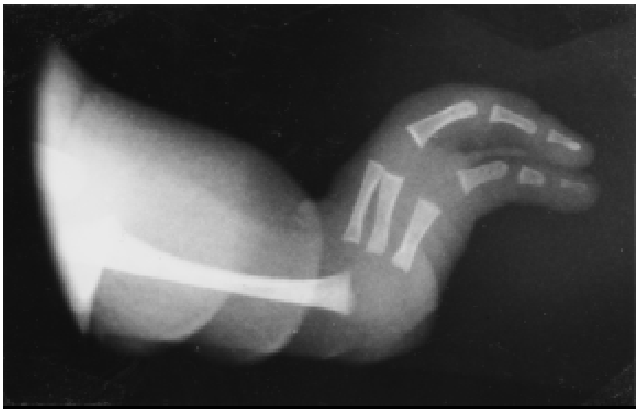

Fig. 2. Radial aplasia with club hand and absent thumb. Absence of the second ray and of phalanges of the fourth digit is also evident.

Fig. 4. Cranial coronal ultrasonography: mild dilatation of the lateral ventricles, more evident on the right side.

chamber through a septal defect was observed. A small hypoplastic left atrium was present, communicating with a large right atrium through the patent foramen ovale. The left atrio-ventricular connection was atretic (Fig. 5).

The autopsy confirmed all these echocardiographic findings and also showed a patent ductus arteriosus, a bicuspid pulmonic valve, and absence of the left pulmonary artery. A single vein coming from the left lung and three veins draining the right lung were normally connected to the left atrium. The left lung appeared unilobulated and supplied by an arterial branch from the ascending aorta. The rest of viscera were normal.

DISCUSSION

We describe an additional case of Goldenhar complex, which is mainly characterized by extrafacial abnormalities, including CNS, cardiovascular system, and upper limbs. The term "oculo-auriculo-vertebral spectrum" (OAVS) is usually employed to indicate an extremely complex and heterogeneous condition. Although microtia, mandibular hypoplasia, vertebral anomalies, and epibulbar dermoid/lipodermoids are considered to be cardinal findings of the condition [Rollnick et al., 1987], its expressivity is quite variable, with ~50% of the patients being affected by other anomalies [Rollnick et al., 1987].

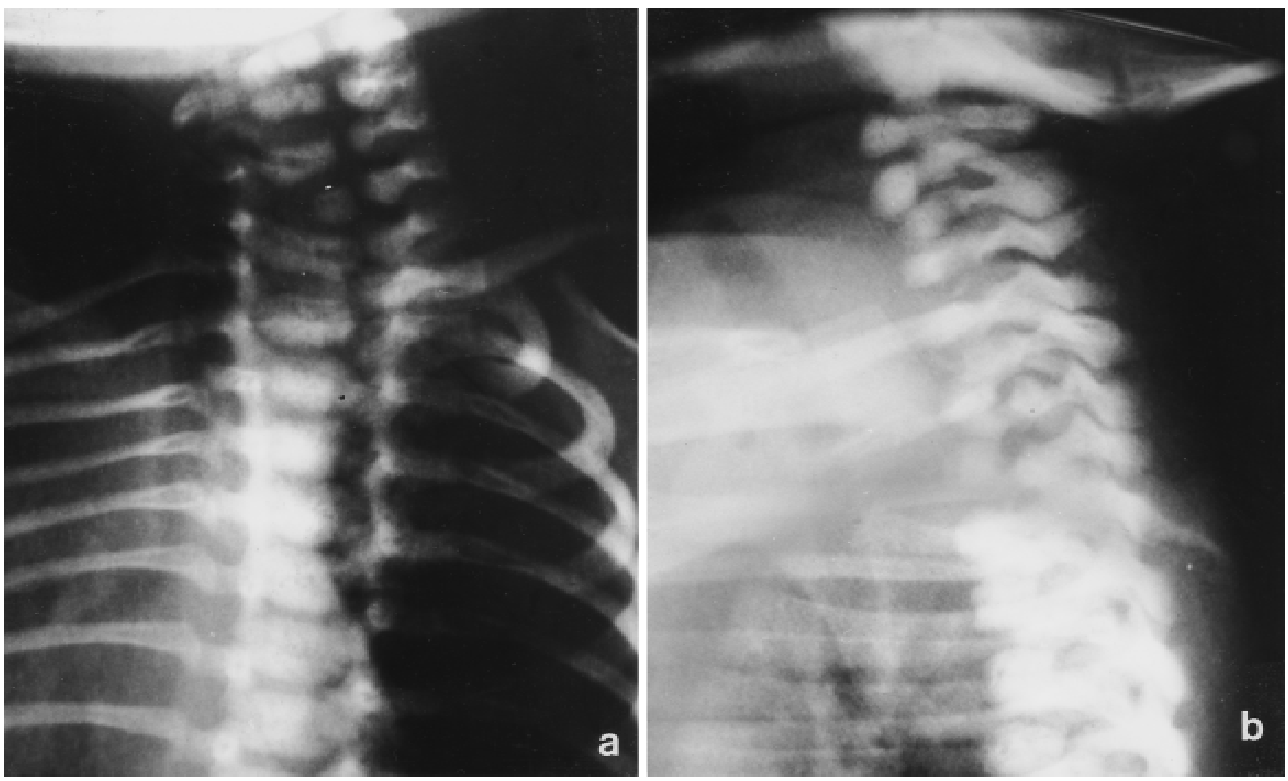

Fig. 3. Frontal (**a**) and lateral (**b**) views of the cervical spine: hemivertebra at C3 with secondary kyphoscoliosis.

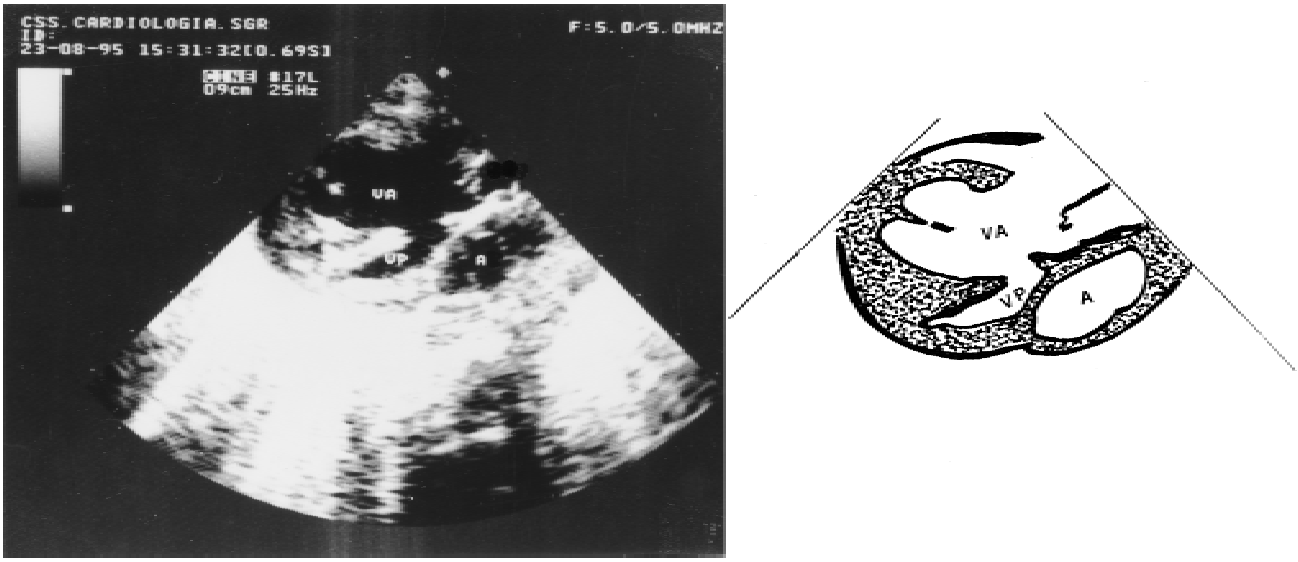

Fig. 5. Two-dimensional, left parasternal long-axis ultrasonography and scheme: the single right-type ventricle (VA) appears partially separated, by the trabecular septum, from a rudimentary left ventricular chamber (VP). The left portion of the enlarged right atrium is posteriorly sided (A).

Facial involvement is evident in 65% of the patients [Smakel, 1986]. Eye and ear abnormalities are present in 50% and 65% of the patients, respectively [Baum, 1973].

The real incidence of extrafacial anomalies, clearly expressed in the present case, is not well known. Eight unrelated Brazilian patients with uncommon and perhaps unique associated anomalies have been recently reported [van Bever et al., 1992]. In the expanded OAVS, the extrafacial findings may be expressed to a greater degree, and this may lead to a different diagnosis. For example, three patients with OAVS and tracheoesophageal anomalies have been described [Sutphen et al., 1995], suggesting the possible presence of other cases of this association not previously specified as OAVS.

Several theories have been suggested to explain the pathogenetic mechanism of the anomalies observed in OAVS. At present there is an apparent agreement that the condition is causally heterogeneous.

Poswillo [1975] hypothesized an early vascular disruption and focal hemorrhage resulting in destruction of differentiating tissues in the first and second branchial arch region [Poswillo, 1975]. Nevertheless, it is very difficult to explain, on the basis of this theory, the extension of the spectrum described above. Subsequently, OAVS has been classified as a defect of blastogenesis, i.e., the time referred to all stages of development during the first 4 weeks of gestation [Opitz, 1993]. In this period, the appearance of the midline, cranial/caudal, right/left, and dorsal/ventral body axes is one of the important processes of gastrulation. According to this theory, some abnormalities shown in our patient, such as ventricular septal defect, might be explained as a midline anomaly secondary to genetic and/or environmental factors. Moreover, most of the defects of our patient are on the left, suggesting that the left side might have been "hit" harder than the right during the earliest stages of R-L development of the embryo. Malformations presumed to be defects of early blastogenesis often occur with increased frequency in monozygotic twinning (MZ) [Opitz, 1993]. Actually, monozygotic twins in Goldenhar complex have been frequently reported and a total of 30 MZ twins and one set of triplets have been collected in two distinct reviews [Boles et al., 1987, Ryan et al., 1988]. More recently, three other probable monozygotic twins have been reported [Rodriguez et al., 1993]. Concordance for the Goldenhar anomaly in certain MZ twins is ~13% (4 out of 30) and the discordance is not surprising considering the nature of twinning [Schinzel et al., 1979].

Molecular bases of congenital malformations are being clarified by studies of the genes expressed in the embryo tissues. In particular, MSX homeobox genes play a critical role for the differentiation of first branchial arch [Takahashi et al., 1992] and cephalic neural crest cells that both contribute to craniofacial development [Robert et al., 1989]. Moreover, manipulations of these genes in mice resulted in defects of structures related to first branchial arch [Satokata et al., 1994].

Additional molecular evidences and cases, like those here reported, enrich the clinical observations, justify the concept of "expanded Goldenhar complex," and may help to clarify the pathogenetic mechanism underlying the condition.

ACKNOWLEDGMENTS

This work was in part supported by ASM-Milano (Associazione Italiana per lo Studio delle Malformazioni).

REFERENCES

Baum JL, Feingold M (1973): Ocular aspects of Goldenhar's syndrome. Am J Ophtalmol 75:250–257.

Boles DJ, Bodurtha J, Nance WE (1987): Goldenhar complex in discordant monozygotic twins: A case report and review of the literature. Am J. Med Genet 28(1):103–109.

Gorlin RJ, Cohen MM, Levin LS (1990): "Syndromes of the Head and Neck." New York: Oxford University Press, pp 641–649.

Opitz JM (1993): Blastogenesis and the "primary field" in human development. BDOAS 29(1):3–37.

Poswillo D (1975): Hemorrage in development of the face. In Bergsma D (ed): "Morphogenesis and Malformation of Face and Brain." New York: Alan R. Liss, for the National Foundation-March of Dimes, BD: OAS XI (7):61–68.

Rollnick BR, Kaye CI, Nagatoshi K, Hauck W, Martin AO (1987): Oculo-auriculovertebral dysplasia and variants phenotypic characteristics of 294 patients. Am J Med Genet 26:361–375.

Robert B, Sassoon D, Jacq B, Gehring W, Buckingham M (1989): Hox-7, a mouse homeobox gene with a novel pattern of expression during embryogenesis. EMBO J 8:91–100.

Rodriguez JI, Palacios J, Lapunzina P (1993): Severe axial anomalies in the oculo-auriculo-vertebral (Goldenhar) complex. Am J Med Genet 47:69–74.

Ryan CA, Finer NN, Ives E (1988): Discordance of signs in monozygotic twins concordant for the Goldenhar anomaly. Am J Med Genet 29:755–761.

Satokata I, Maas R (1994): Msx1 deficient mice exhibit cleft palate and abnormalities of craniofacial and tooth development. Nat Genet 6:348–356.

Schinzel AAGL, Smith DW, Miller JR (1979): Monozygotic twinning and structural defects. J Ped 95:921–930.

Smakel Z (1986): Craniofacial changes in hemifacial microsomia. J Craniofac Genet Develop Biol 6:151–170.

Sutphen R, Galan-Gomez E, Cortada X, Newkirk PN, Kousseff BG: (1995). Tracheoesophageal anomalies in oculoauriculovertebral (Goldenhar) spectrum. Clin Genet 48:66–71.

Takahashi Y, Monsoro-Burg A-H, Bontoux M, Le Douarin NM: (1992): A role for Quox-8 in the establishment of the dorsoventral pattern during vertebrate development. Proc Natl Acad Sci USA 89:10237–10241.

Van Bever Y, Van den Ende JJ, and Richieri Costa A (1992): Oculo-auriculovertebral complex and uncommon associated anomalies: Report on 8 unrelated Brazilian patients. Am J Med Genet 44:683–690.